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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

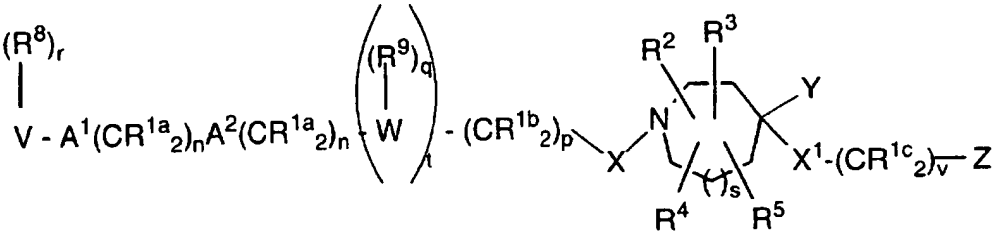
The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises piperidine-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formula A:



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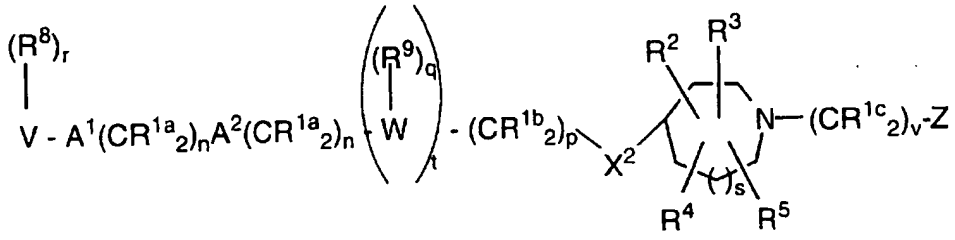
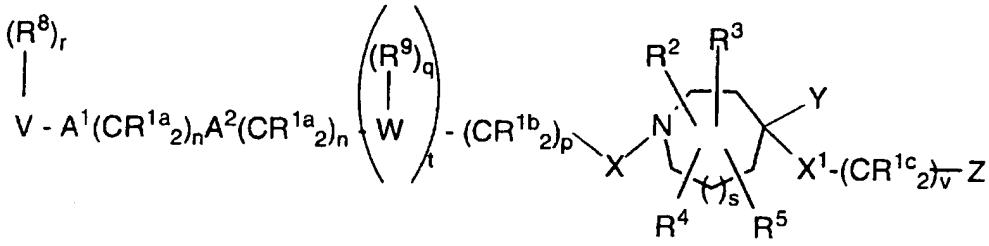


B

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:



A

wherein:

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

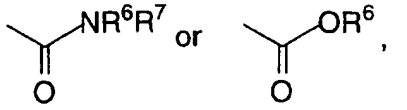
R^{1c} is selected from:

a) hydrogen,

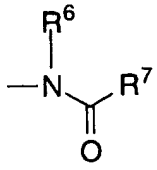
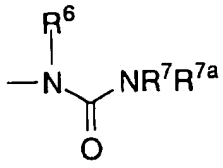
b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-,

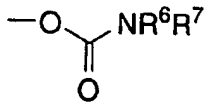
$R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

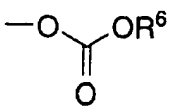
c) unsubstituted or substituted aryl;

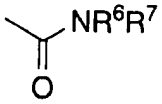
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, OR^{10},  ,

wherein the substituted group is substituted with one or more of:

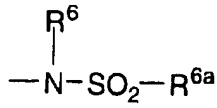
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5)  ,
6)  ,
7)  ,

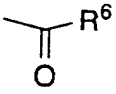
8)  ,

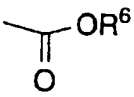
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form $-(CH_2)_u-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and $-N(COR^{10})-$;

R^4 and R^5 are independently selected from H and CH_3;

and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom;

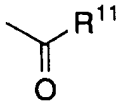
R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl or substituted heterocycle,

c) halogen,

d) HO,

e) 

f) $-SO_2R^{11}$, or

g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

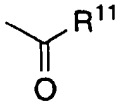
R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e) 

f) $-SO_2R^{11}$, or

g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)m$-,

$R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

R^{12} is selected from: H; unsubstituted or substituted $C_{1\text{-}8}$ alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle, wherein the substituted alkyl, substituted aryl or substituted heterocycle is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) $C_{1\text{-}4}$ alkyl,
   b) $(CH_2)_pOR^6$,

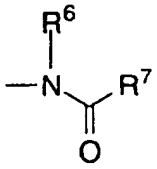
c) $(CH_2)_pNR^6R^7$,
d) halogen,
e) CN,
f) aryl or heteroaryl,
g) perfluoro-C1-4 alkyl,
h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

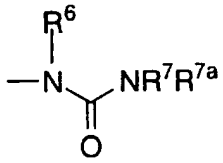
2) C3-6 cycloalkyl,

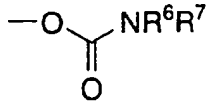
3) OR^6,

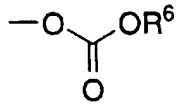
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

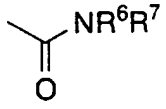
5) $-NR^6R^7$,

6)  ,

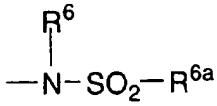
7)  ,

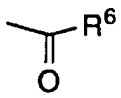
8)  ,

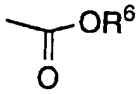
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F,

17) perfluoro-C_{1-4}-alkyl, or

18) C_{1-6}-alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)2N(R^{10})-, -N(R^{10})S(O)2-, or S(O)m;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)m;

W is a heterocycle;

X is a bond, -CH_2-, -C(=O)-, -NR^6C(=O)- or -S(=O)m-;

X^1 is a bond, -C(=O)-, -NR^6C(=O)-, -NR^6-, -O- or -S(=O)m-;

Y is selected from:

a) hydrogen,

b) $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{12}C(O)$-, $R^{10}OC(O)$-, N_3, F, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, $R^{10}C(O)$- and $R^{10}OC(O)$-;

Z is an unsubstituted or substituted group selected from aryl and heterocycle, wherein the substituted group is substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) -$S(O)_mR^{6a}$, or
   g) -$C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) -$S(O)_mR^{6a}$,
10) -$C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

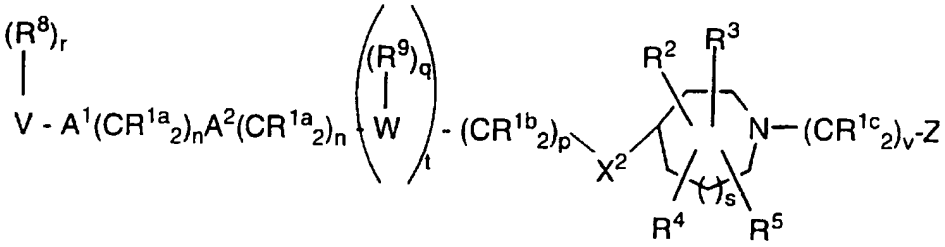
p is 0, 1, 2, 3 or 4;

q is 1 or 2;

	r is	0 to 5, provided that r is 0 when V is hydrogen;
	s is	0 or 1;
	t is	0 or 1;
	u is	4 or 5; and
5	v is	0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In a second embodiment of this invention, the inhibitors of
10 farnesyl-protein transferase are illustrated by the formula B:



B

15 wherein:

R^{1a} and R^{1b} are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-
20 C(O)-, CN, NO_2, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-,

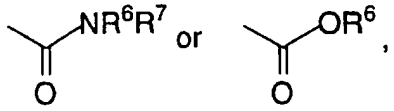
c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10}
25 cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-;

R^{1c} is selected from:

a) hydrogen,

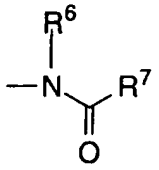
b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

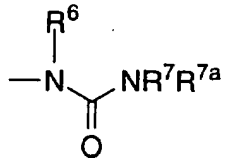
c) unsubstituted or substituted aryl;

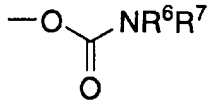
R^2 and R^3 are independently selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, OR^{10},  wherein the substituted group is substituted with one or more of:

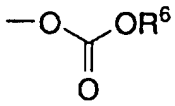
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

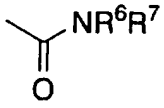
5) $-NR^6R^7$,

6)  ,

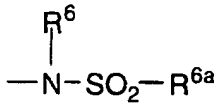
7)  ,

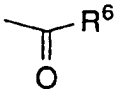
8)  ,

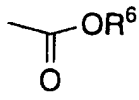
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F, or

17) perfluoro-C_{1-4}-alkyl; or

R^2 and R^3 are attached to the same C atom and are combined to form -$(CH_2)_u$ - wherein one of the carbon atoms is optionally replaced by a moiety selected from: O, $S(O)_m$, -NC(O)-, and -$N(COR^{10})$- ;

R^4 and R^5 are independently selected from H and CH_3;

and any two of R^2, R^3, R^4 and R^5 are optionally attached to the same carbon atom;

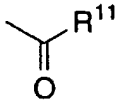
R^6, R^7 and R^{7a} are independently selected from: H; C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) unsubstituted aryl, substituted aryl, unsubstituted heteroaryl or substituted heterocycle,

c) halogen,

d) HO,

e) 

f) $-SO_2R^{11}$, or

g) $N(R^{10})_2$; or

R^6 and R^7 may be joined in a ring;
R^7 and R^{7a} may be joined in a ring;

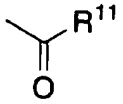
R^{6a} is selected from: C_{1-4} alkyl, C_{3-6} cycloalkyl, heterocycle, aryl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e) 

f) $-SO_2R^{11}$, or

g) $N(R^{10})_2$;

R^8 is independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, cyanophenyl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NH$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{10}OC(O)NH$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, NO_2, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2NC(O)$-, $R^{10}{}_2N$-$C(NR^{10})$-, CN, $R^{10}C(O)$-, N_3, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)$_2$N(R^{10})-, -N(R^{10})S(O)$_2$-, or S(O)$_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

W is a heterocycle;

X^2 is a bond, -CH_2-, -C(=O)-, -NR^6C(=O)-, -C(=O)NR^6-, -NR^6-, -O- or -S(=O)$_m$-;

Z is an unsubstituted or substituted group selected from aryl and heterocycle, wherein the substituted group is substituted with one or more of the following:

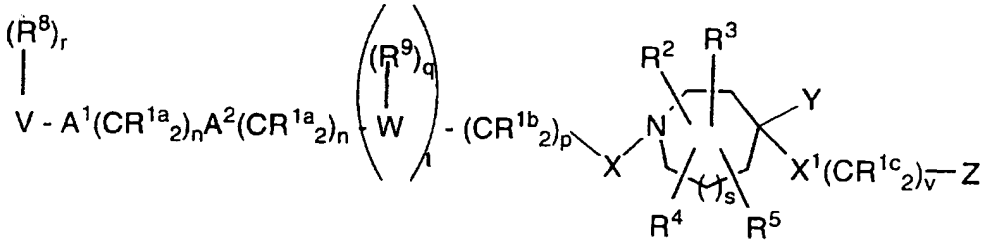
1) C_1-$_4$ alkyl, unsubstituted or substituted with:
   a) C_1-$_4$ alkoxy,
   b) NR^6R^7,
   c) C_3-$_6$ cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) -S(O)$_m$$R^{6a}$, or
   g) -C(O)NR^6R^7,
2) aryl or heterocycle,

3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
q is 1 or 2;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 0 or 1;
u is 4 or 5; and
v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the compounds of this invention is illustrated by the following formula A:



A

wherein:

R^{1a} is independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and $-N(R^{10})_2$;

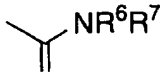
R^{1c} is selected from:

a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, $-N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

R^3, R^4 and R^5 are independently selected from H and CH_3;

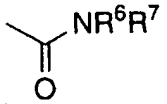
R^2 is H; OR^{10},  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)  ;

and any two of R^2, R^3, R^4, and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,

b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

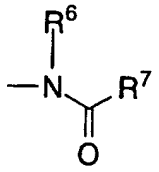
R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

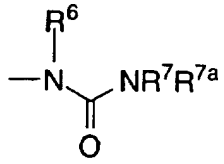
R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle,

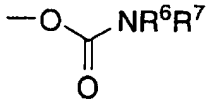
wherein the substituted alkyl, suvbstituted aryl or substituted heterocycle is substituted with one or more of:

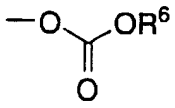
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

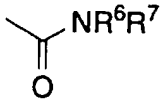
5) $-NR^6R^7$,

6)  ,

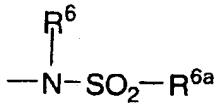
7)  ,

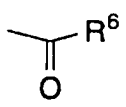
8)  ,

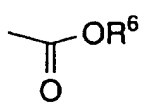
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F,

17) perfluoro-C_{1-4}-alkyl, or

18) C_{1-6}-alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X is -CH_2- or -C(=O)-;

X^1 is a bond, -C(=O)-, -NR^6C(=O)-, -NR^6-, -O- or -$S(=O)_m$-;

Y is selected from:

a) hydrogen,

b) $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{12}C(O)$-, $R^{10}OC(O)$-, N_3, F, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, $R^{10}C(O)$- and $R^{10}OC(O)$-;

Z is an unsubstituted or substituted group selected from aryl and heterocycle, wherein the substituted group is substituted with one or more of the following:

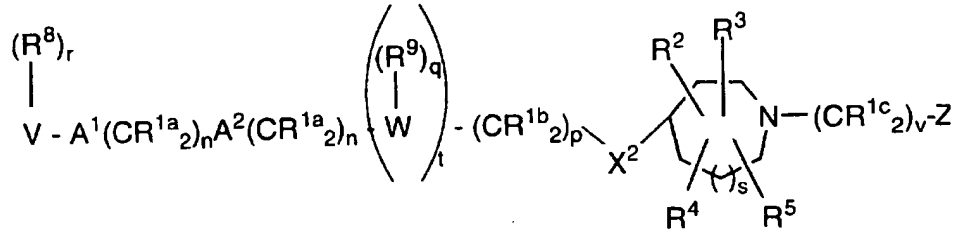
1) C_1-4 alkyl, unsubstituted or substituted with:
   a) C_1-4 alkoxy,
   b) NR^6R^7,
   c) C_3-6 cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) -$S(O)_mR^{6a}$, or
   g) -$C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) -$S(O)_mR^{6a}$,
10) -$C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

	m is	0, 1 or 2;
	n is	0, 1, 2, 3 or 4;
	p is	0, 1, 2, 3 or 4;
5	r is	0 to 5, provided that r is 0 when V is hydrogen;
	s is	0 or 1;
	t is	1; and
	v is	0, 1 or 2;

10 or a pharmaceutically acceptable salt thereof.

In a another preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula B:

15



B

wherein:

20

R^{1a} is independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

25 b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from

unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$- and -$N(R^{10})_2$;

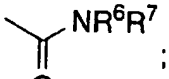
R^{1c} is selected from:

a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

R^3, R^4 and R^5 are independently selected from H and CH_3;

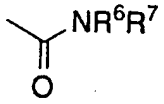
R^2 is H;  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)  ;

and any two of R^2, R^3, R^4, and R^5 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl,
unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^9 is selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, CN, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

X^2 is a bond, -CH_2-, -C(=O)-, -NR^6C(=O)-, -C(=O)NR^6-, -NR^6-, -O- or -$S(=O)_m$-;

Z is an unsubstituted or substituted aryl , wherein the substituted aryl is substituted with one or more of the following:

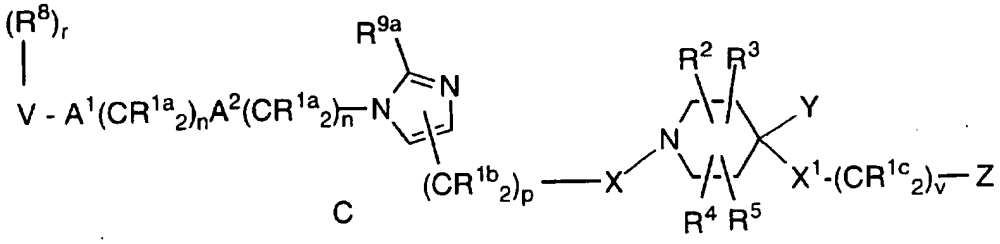
1) C_1-4 alkyl, unsubstituted or substituted with:
   a) C_1-4 alkoxy,
   b) NR^6R^7,
   c) C_3-6 cycloalkyl,
   d) aryl, substituted aryl or heterocycle,

e) HO,
f) $-S(O)_mR^{6a}$, or
g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen;
s is 0 or 1;
t is 1; and
v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

A further preferred embodiment of the compounds of this invention are illustrated by the formula C:



C

wherein:

R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

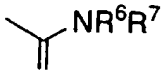
R^{1c} is selected from:

a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

R^3 and R^4 independently selected from H and CH_3;

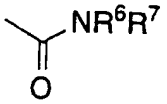
R^2 is selected from H; OR^{10};  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5)  ;

and R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

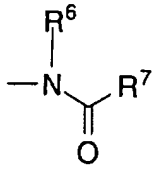
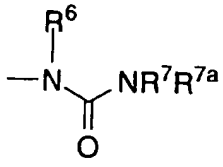
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

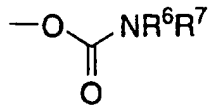
R^{9a} is hydrogen or methyl;

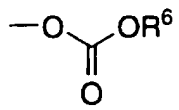
R^{10} is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

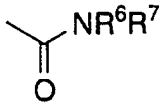
R^{11} is independently selected from C_1-C_6 alkyl and aryl;

R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle, wherein the substituted alkyl, substituted aryl or substituted heterocycle is substituted with one or more of:

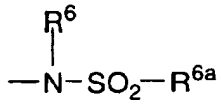
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
   e) CN,
   f) aryl or heteroaryl,
   g) perfluoro-C_{1-4} alkyl,
   h) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},
5) $-NR^6R^7$,
6)  ,
7)  ,

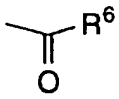
8)  ,

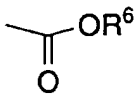
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3,

16) F,

17) perfluoro-C_{1-4}-alkyl, or

18) C_{1-6}-alkyl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, or S(O)m;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

X is $-CH_2-$ or -C(=O)-;

X^1 is a bond, $-C(=O)-$, $-NR^6C(=O)-$, $-NR^6-$, -O- or $-S(=O)_m-$;

Y is selected from:

a) hydrogen,

b) $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, CN, NO_2, $(R^{10})_2N-C(NR^{10})-$, $R^{12}C(O)-$, $R^{10}OC(O)-$, N_3, F, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, $R^{10}C(O)-$ and $R^{10}OC(O)-$;

Z is an unsubstituted or substituted aryl, wherein the substituted aryl is substituted with one or more of the following:

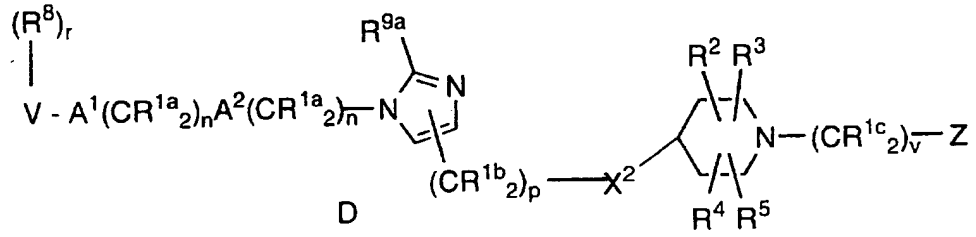
1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^{6a}$, or

g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen; and
v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

Another further preferred embodiment of the compounds of this invention are illustrated by the formula D:



D

wherein:

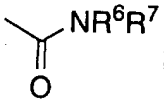
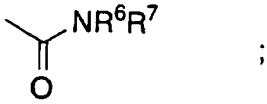
R^{1a} is selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

R^{1c} is selected from:
a) hydrogen,
b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and
c) unsubstituted or substituted aryl;

R^3 and R^4 independently selected from H and CH_3;

R^2 is selected from H; OR^{10};  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:
1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or
5)  ;

and R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6 and R^7 are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) halogen, or

c) aryl or heterocycle;

R^8 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{9a} is hydrogen or methyl;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-,

-C(O)-, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, or S(O)$_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C$_1$-C$_{20}$ alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

e) C$_2$-C$_{20}$ alkenyl, and

provided that V is not hydrogen if A^1 is S(O)$_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)$_m$;

X^2 is a bond, -CH$_2$-, -C(=O)-, -NR^{6}C(=O)-, -C(=O)NR^6-, -NR^6-, -O- or -S(=O)$_m$-;

Z is an unsubstituted or substituted aryl, wherein the substituted aryl is substituted with one or more of the following:

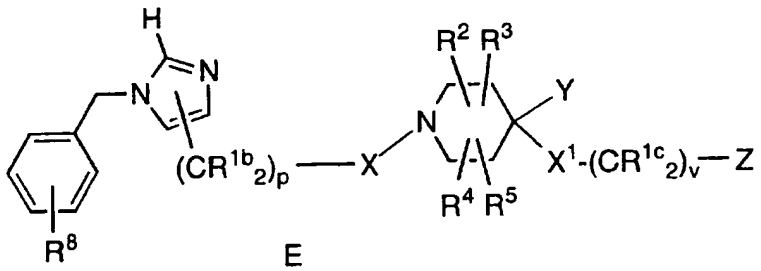
1) C$_{1-4}$ alkyl, unsubstituted or substituted with:
   a) C$_{1-4}$ alkoxy,
   b) NR^{6}R^7,
   c) C$_{3-6}$ cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) -S(O)$_m$R^{6a}, or
   g) -C(O)NR^{6}R^7,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^{6}R^7,
6) CN,

7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4; and
r is 0 to 5, provided that r is 0 when V is hydrogen; and
v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:



E

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, $-N(R^{10})_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or $-N(R^{10})_2$;

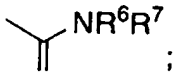
R^{1c} is selected from:

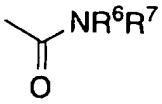
a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

R^3 and R^4 independently selected from H and CH_3;

R^2 is selected from H; OR^{10};  ; or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,
2) heterocycle,
3) OR^6,
4) SR^{6a}, SO_2R^{6a}, or
5)  ;

and R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from:

H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:

C_{1-4} alkyl or C_{3-6} cycloalkyl,
unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

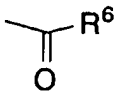
R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

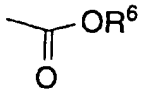
R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle, wherein the substituted alkyl, suvbstituted aryl or substituted heterocycle is substituted with one or more of:
1) aryl or heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkyl,
b) halogen,
c) CN,
d) perfluoro-C_{1-4} alkyl,
2) C_{3-6} cycloalkyl,
3) OR^6,

4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

5)  ,

6)  ,

7) N_3,

8) F,

9) perfluoro-C_{1-4}-alkyl, or

10) C_{1-6}-alkyl;

X is $-CH_2-$ or $-C(=O)-$;

X^1 is a bond, $-C(=O)-$ or $-S(=O)_m-$;

Y is selected from:

a) hydrogen,

b) $R^{10}O-$, $R^{11}S(O)_m-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, CN, NO_2, $(R^{10})_2N-C(NR^{10})-$, $R^{12}C(O)-$, $R^{10}OC(O)-$, N_3, F, $-N(R^{10})_2$, or $R^{11}OC(O)NR^{10}-$,

c) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, $R^{10}O-$, $R^{10}C(O)NR^{10}-$, $(R^{10})_2N-C(O)-$, $R^{10}C(O)-$ and $R^{10}OC(O)-$;

Z is an unsubstituted or substituted aryl, wherein the substituted aryl is substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:

a) C_{1-4} alkoxy,

b) NR^6R^7,

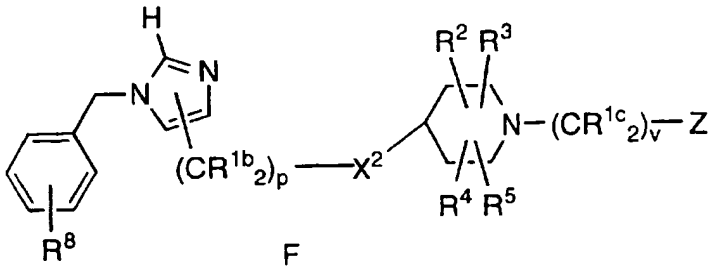
c) C_{3-6} cycloalkyl,
d) aryl, substituted aryl or heterocycle,
e) HO,
f) $-S(O)_mR^{6a}$, or
g) $-C(O)NR^6R^7$,

2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4; and
v is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

In another embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula F:



F

wherein:

R^{1b} is independently selected from:

a) hydrogen,

b) aryl, heterocycle, cycloalkyl, $R^{10}O$-, -$N(R^{10})_2$ or C_2-C_6 alkenyl,

c) C_1-C_6 alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, cycloalkyl, alkenyl, $R^{10}O$-, or -$N(R^{10})_2$;

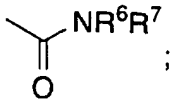
R^{1c} is selected from:

a) hydrogen,

b) unsubstituted or substituted C_1-C_6 alkyl wherein the substitutent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $R^{10}O$-, $R^{11}S(O)_m$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-C(O)-, CN, $(R^{10})_2N$-C(NR^{10})-, $R^{10}C(O)$-, $R^{10}OC(O)$-, N_3, -$N(R^{10})_2$, and $R^{11}OC(O)$-NR^{10}-, and

c) unsubstituted or substituted aryl;

R^3 and R^4 independently selected from H and CH_3;

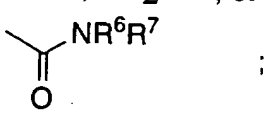
R^2 is selected from H; OR^{10};  or C_{1-5} alkyl, unbranched or branched, unsubstituted or substituted with one or more of:

1) aryl,

2) heterocycle,

3) OR^6,

4) SR^{6a}, SO_2R^{6a}, or

5) 

and R^2, R^3 and R^4 are optionally attached to the same carbon atom;

R^6, R^7 and R^{7a} are independently selected from:
H; C_{1-4} alkyl, C_{3-6} cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^{6a} is selected from:
C_{1-4} alkyl or C_{3-6} cycloalkyl, unsubstituted or substituted with:
a) C_{1-4} alkoxy,
b) halogen, or
c) aryl or heterocycle;

R^8 is independently selected from:
a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, CN, NO_2, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-, and
c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, $R^{10}O$-, $R^{10}C(O)NR^{10}$-, $(R^{10})_2N$-$C(NR^{10})$-, $R^{10}C(O)$-, $R^{10}OC(O)$-, -$N(R^{10})_2$, or $R^{11}OC(O)NR^{10}$-;

R^{10} is independently selected from hydrogen, C_1-C_{14} alkyl, substituted or unsubstituted benzyl and substituted or unsubstituted aryl;

R^{11} is independently selected from C_1-C_6 alkyl and substituted or unsubstituted aryl;

X^2 is -CH_2-, -C(=O)-, -C(=O)NR^6- or -NR^6-;

Z is an unsubstituted or substituted aryl, wherein the substituted aryl is substituted with one or more of the following:

1) C_{1-4} alkyl, unsubstituted or substituted with:
   a) C_{1-4} alkoxy,
   b) NR^6R^7,
   c) C_{3-6} cycloalkyl,
   d) aryl, substituted aryl or heterocycle,
   e) HO,
   f) $-S(O)_mR^{6a}$, or
   g) $-C(O)NR^6R^7$,
2) aryl or heterocycle,
3) halogen,
4) OR^6,
5) NR^6R^7,
6) CN,
7) NO_2,
8) CF_3;
9) $-S(O)_mR^{6a}$,
10) $-C(O)NR^6R^7$, or
11) C_3-C_6 cycloalkyl;

m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4; and
v is 0, 1 or 2;

or the pharmaceutically acceptable salts thereof.

The preferred compounds of this invention are as follows:

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-methylphenyl)-4-hydroxy piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-chlorophenyl)-4 hydroxy piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(2-methylbenzyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-methylphenyl)-4 hydroxy piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(2-methylbenzyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(4-methylbenzyl))isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(3-methylbenzyl))isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(2,4-dichlorobenzyl))isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(3-methoxybenzyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(1-naphthylmethyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(4-chlorobenzyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-(2,3-dichlorobenzyl)isonipecotic acid methyl ester,

N-{1-(4 Cyanobenzyl)-1H-imidazol-5-yl-aminocarbonyl}-4-(2-methylbenzyl) isonipecotic acid methyl ester,

2(R,S)-N{-2-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]2-(4-cyanobenzyl)} acetyl-4-(2-methylbenzyl)-isonipecotic acid methyl ester,

N-{[1-(Naphth-2-ylmethyl)-1H-imidazol-5-yl]acetyl}-4-(2-methylbenzyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-methoxymethyl-4-(2-methylbenzyl) piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}--4-methoxymethyl-4-(2-methylbenzyl) piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetyl}-4-hydroxymethyl-4-(2-methylbenzyl) piperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]ethyl}-4-(2-methylbenzyl)isonipecotic acid methyl ester,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl} -*trans*-4-(3-methylphenyl)-3-hydroxypiperidine,

N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl} -*trans*-4- (3-methylphenyl)-3 methoxy piperidine,

N-{[1-(4-cyanobenzyl)-1H-imidazol-5-yl]methyl} -*trans*-4- (3-methylphenyl)-3 benzyloxy piperidine,

1-[2(R,S)-Amino-3-(2-tetradecyloxyphenyl)propyl]-4-(2-methylbenzyl)isonipecotic acid methyl ester,

N-2-(S)-aminolauroyl-4-(1-napthylmethyl) isonipecotic acid methyl ester,

4-(Benzoxazolidin-2-one-1-yl)-1-[1-(4-cyanobenzyl)-5-imidazolylacetyl]piperidine,

4-(1,2-Dihydro-4(H)-3,1-benzoxazin-2-one-1-yl)-1-[1-(4-cyanobenzyl)-5-imidazolylacetyl]piperidine,

4-(1,2-Dihydro-4(H)-3,1-benzoxazin-2-one-1-yl)-1-[1-(4-cyanobenzyl)-5-imidazolylmethyl]piperidine,

N-[2-{(4-Cyanobenzyl)-5-imidazolyl}ethyl]-4-carbamoyl-1-phenylpiperidine

4-[2-{1-(4-Cyanobenzyl)-5-imidazolyl}ethyl]-1-phenylpiperidine

4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-trifluoromethylbenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-trifluoromethylbenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2-trifluoromethylbenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2-methylbenzyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-methylbenzyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-methylbenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-(5-{2-[4-Hydroxymethyl-4-(3-methylbenzyl)piperidine-1-yl]-2-oxoethyl}imidazol-1-ylmethyl)benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-methylbenzyl)piperidine-1-carbonyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2-methylbenzyl)piperidine-1-carbonyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2-cyanobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-cyanobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(4-cyanobenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2,5-dimethylbenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2,5-dichlorobenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(3,5-dimethylbenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-(5-{4-Hydroxymethyl-4-[3,5-bis(trifluoromethyl)benzyl]-piperidine-1-ylmethyl}-2-methylimidazol-1-ylmethyl)benzonitrile

4-{5-[4-Hydroxymethyl-4-(2,3-dichlorobenzyl)piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-[5-(4-Hydroxymethyl-4-benzylpiperidine-1-ylmethyl)-2-methylimidazol-1-ylmethyl]benzonitrile

4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzamide

4-{5-[4-Methoxymethyl-4-(3-methylbenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-methylbenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(2-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(2-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-cyanobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-(5-{2-[4-Methoxymethyl-4-(3-methylbenzyl)-piperidine-1-yl]-2-oxoethyl}imidazol-1-ylmethyl)benzonitrile

4-{5-[4-Methoxymethyl-4-(3-methylbenzyl)piperidine-1-carbonyl]imidazol-1-ylmethyl}benzonitrile

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylbenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-trifluoromethoxybenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-2-methyl-3H-imidazol-4-ylmethyl]-4-(3-trifluoromethoxybenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(2-trifluoromethoxybenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-cyanobenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-[3-(benzyloxycarbonylaminomethyl)benzyl]piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-[3-(aminomethyl)benzyl]piperidine-4-carboxylate

Ethyl 1-[3-(4-cyanobenzyl)-2-methyl-3H-imidazol-4-ylmethyl]-4-[3-(methanesulfonylaminomethyl)benzyl]piperidine-4-carboxylate

Ethyl 1-[3-(4-cyanobenzyl)-2-methyl-3H-imidazol-4-ylmethyl]-4-(3-nitrobenzyl)piperidine-4-carboxylate

Ethyl 1-[3-(4-cyanobenzyl)-2-methyl-3H-imidazol-4-ylmethyl]-4-(3-methanesulfonylaminobenzyl)piperidine-4-carboxylate

Ethyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-benzylpiperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-cyclopropylmethylpiperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylcarbonyl]-4-(3-methylbenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylcarbonyl]-4-(2-methylbenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(3-trifluoromethoxybenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(2-trifluoromethoxybenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(3-cyanobenzyl)piperidine-4-carboxylate

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylethyl]-4-(3-methylbenzyl)piperidine-4-carboxylate

(±) Methyl 2-(n-butyl)-1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylbenzyl)piperidine-4-carboxylate

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylbenzyl)isonipecotamide

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(2-methylbenzyl)isonipecotamide

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(3-methyl-benzyl)isonipecotamide

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(2-methyl-benzyl)isonipecotamide

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylcarbonyl]-4-(3-methyl-benzyl)isonipecotamide

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylcarbonyl]-4-(2-methyl-benzyl)isonipecotamide

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(2-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(4-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-2-methyl-3H-imidazol-4-ylmethyl]-4-(3-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylcarbonyl]-4-(3-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylcarbonyl]-4-(2-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(3-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylacetyl]-4-(2-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylethyl]-4-(3-methylbenzyl)piperidine-4-carbonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylethyl]-4-(2-methylbenzyl)piperidine-4-carbonitrile

4-{5-[4-Hydroxymethyl-4-(4-methylpyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(6-methylpyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(2-methylpyridin-4-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(6-methylpyridin-2-ylmethyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Hydroxymethyl-4-(6-hydroxypyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile

4-[5-(4-Hydroxymethyl-4-quinolin-2-ylmethyl-piperidine-1-ylmethyl)-2-methylimidazol-1-ylmethyl]benzonitrile

Methyl 1-[3-(4-cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylbenzoyl)piperidine-4-carboxylate

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylbenzoyl)piperidine

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(hydroxy-m-tolylmethyl)piperidine

4-{5-[4-Hydroxymethyl-4-(3-tolylsulfanyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-tolylsulfanyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-tolylsulfinyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-Methoxymethyl-4-(3-tolylsulfonyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylphenylamino)isonipecotamide

Ethyl 1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylphenylamino)piperidine-4-carboxylate

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-hydroxymethyl-4-(3-methylphenylamino)piperidine

O-{1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylphenylamino)piperidyl-4-methyl}carbamate

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylphenylamino)piperidyl-4-methylurea

1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylphenylamino)piperidyl-4-methylsulfamide

4-{5-[4-(Hydroxydiphenylmethyl)piperidin-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile

4-{5-[4-(Hydroxydiphenylmethyl)piperidine-1-carbonyl]imidazol-1-ylmethyl}benzonitrile

4-(5-{2-[4-(Hydroxydiphenylmethyl)piperidin-1-yl]-2-oxoethyl}-3H-imidazol-1-ylmethyl)benzonitrile

1-(Piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(1-Phenylpiperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(1-(2-Methylphenyl)piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(1-(2-Chlorobenzoyl)piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(1-(3-Chlorobenzoyl)piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(1-(3-Chlorobenzenesulfonyl)piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

1-(1-(3-Chlorobenzyl)piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole

2-[3-(4-Cyanobenzyl)-3H-imidazol-1-yl]-N-(1-phenylpiperidin-4-yl)acetamide

2-[3-(4-Cyanobenzyl)-3H-imidazol-1-yl]-N-benzyl-N-(1-phenylpiperidin-4-yl)acetamide

2-[3-(4-Cyanobenzyl)-3H-imidazol-1-yl]-N-(1-phenylpiperidin-4-yl)-N-pyridin-4-ylmethylacetamide

2-[3-(4-Cyanobenzyl)-3H-imidazol-1-yl]-N-phenethyl-N-(1-phenylpiperidin-4-yl)acetamide

4-{5-[(1-Phenylpiperidin-4-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile

4-(5-{[Benzyl(1-phenylpiperidin-4-yl)amino]methyl}imidazol-1-ylmethyl)benzonitrile

4-(5-{[(1-Phenylpiperidin-4-yl)pyridin-4-ylmethylamino]methyl}imidazol-1-ylmethyl)benzonitrile

4-(5-{[Phenethyl(1-phenylpiperidin-4-yl)amino]methyl}imidazol-1-ylmethyl)benzonitrile

4-{5-[2-(1-Phenylpiperidin-4-ylamino)ethyl]imidazol-1-ylmethyl}benzonitrile

4-(5-{2-[Benzyl(1-phenylpiperidin-4-yl)amino]ethyl}imidazol-1-ylmethyl)benzonitrile

2-[3-(4-Cyanobenzyl)-3H-imidazol-1-yl]-N-(4-cyanobenzyl)-N-(1-phenylpiperidin-4-yl)acetamide

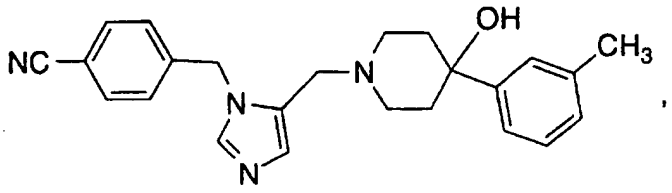
N-(1-Benzylpiperidin-4-yl)-2-[3-(4-cyanobenzyl)-3H-imidazol-4-yl]acetamide and

4-{5-[(1-Benzylpiperidin-4-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile

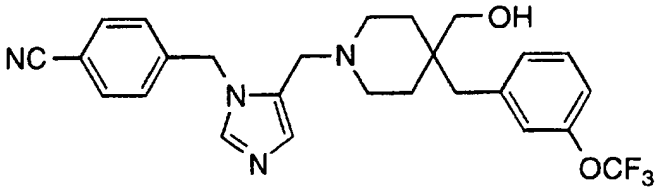
or a pharmaceutically acceptable salt thereof.

Specific examples of the compounds of the invention are:

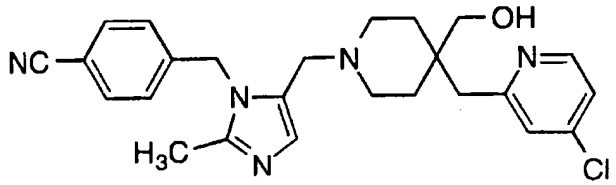
N-{[1-(4-Cyanobenzyl)-1H-imidazol-5-yl]methyl}-4-(3-methylphenyl)-4-hydroxy piperidine



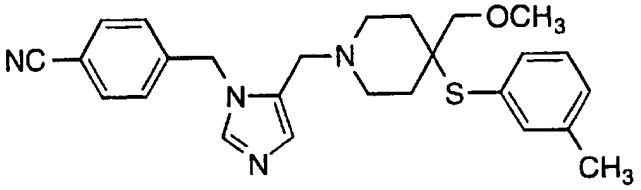
4-{5-[4-Hydroxymethyl-4-(3-trifluoromethoxybenzyl)-piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile



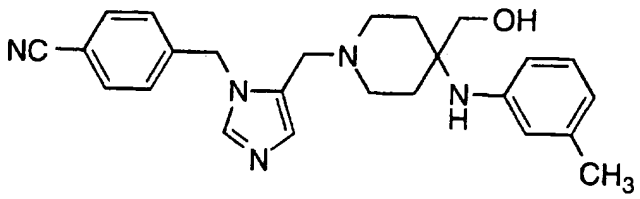
4-{5-[4-Hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile



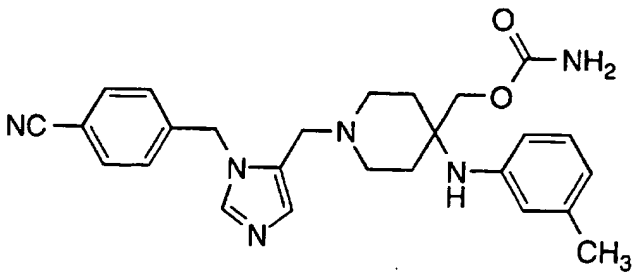
4-{5-[4-Methoxymethyl-4-(3-tolylsulfanyl)piperidine-1-ylmethyl]imidazol-1-ylmethyl}benzonitrile trifluoroacetate salt



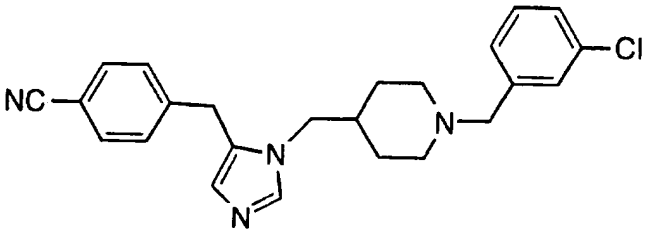
1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-hydroxymethyl-4-(3-methylphenylamino)piperidine



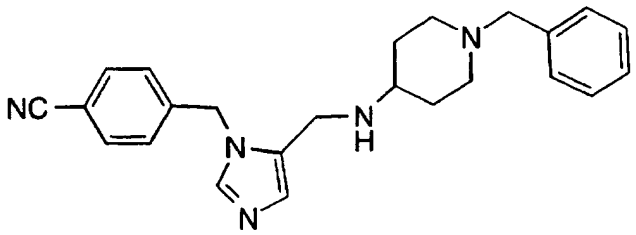
1-[3-(4-Cyanobenzyl)-3H-imidazol-4-ylmethyl]-4-(3-methylphenylamino)-piperidyl-4-methylcarbamate



1-(1-(3-Chlorobenzoyl)piperidin-4-ylmethyl)-5-(4-cyanobenzyl)imidazole



4-{5-[(1-Benzylpiperidin-4-ylamino)methyl]imidazol-1-ylmethyl}benzonitrile



or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^1, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may

be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, benzoxazolidinonyl, benzoxazinonyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

As used herein in the definition of R^2 and R^3, the term "the substituted group" intended to mean a substituted C_{1-8} alkyl, substituted

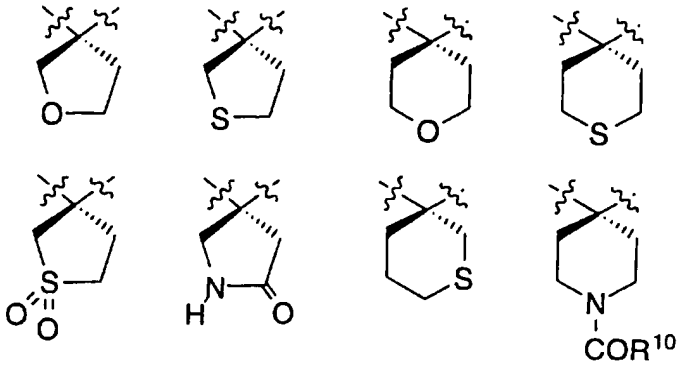
C_{2-8} alkenyl, substituted C_{2-8} alkynyl, substituted aryl or substituted heterocycle from which the substitutent(s) R^2 and R^3 are selected.

As used herein in the definition of R^6, R^7 and R^{7a}, the substituted C_{1-8} alkyl, substituted C_{3-6} alkenyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted arylsulfonyl, substituted heteroarylsulfonyl and substituted heterocycle include moieties containing from 1 to 3 substitutents in addition to the point of attachment to the rest of the compound.

As used herein, when no specific substituents are set forth, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group which is substituted on a substitutable ring carbon atom with 1 or 2 substitutents selected from the group which includes but is not limited to F, Cl, Br, CF_3, NH_2, $N(C_1\text{-}C_6$ alkyl$)_2$, NO_2, CN, $(C_1\text{-}C_6$ alkyl$)O$-, -OH, $(C_1\text{-}C_6$ alkyl$)S(O)_m$-, $(C_1\text{-}C_6$ alkyl$)C(O)NH$-, $H_2N\text{-}C(NH)$-, $(C_1\text{-}C_6$ alkyl$)C(O)$-, $(C_1\text{-}C_6$ alkyl$)OC(O)$-, N_3,$(C_1\text{-}C_6$ alkyl$)OC(O)NH$-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and $C_1\text{-}C_{20}$ alkyl.

When R^2 and R^3 are combined to form - $(CH_2)_u$ -, cyclic moieties are formed. Examples of such cyclic moieties include, but are not limited to:

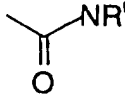
In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



Lines drawn into the ring systems from substituents (such as from R^2, R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, $-N(R^{10})_2$, $R^{10}C(O)NR^{10}$- or unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, $-N(R^{10})_2$, $R^{10}O$- and $R^{10}C(O)NR^{10}$-. More preferably, R^{1a} and R^{1b} are independently selected from: hydrogen or unsubstituted or substituted C_1-C_6 alkyl wherein the substituent on the substituted C_1-C_6 alkyl is selected from unsubstituted or substituted phenyl, $-N(R^{10})_2$, $R^{10}O$- and $R^{10}C(O)NR^{10}$-.

Preferably, R^2 is selected from: H, OR^{10},



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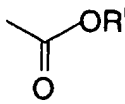


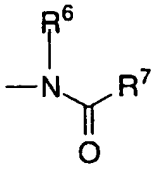
,

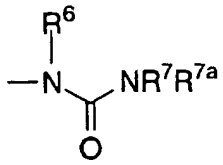
and an unsubstituted or substituted group, the group selected from C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl;

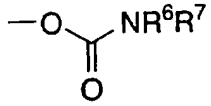
wherein the substituted group is substituted with one or more of:

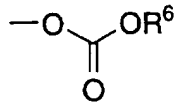
1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) $(CH_2)_pOR^6$,
   c) $(CH_2)_pNR^6R^7$,
   d) halogen,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, SO_2R^{6a},

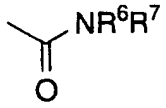
5) $-NR^6R^7$,

6)  ,

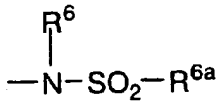
7)  ,

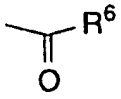
8)  ,

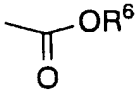
9)  ,

10)  ,

11) $-SO_2-NR^6R^7$,

12)  ,

13)  ,

14)  ,

15) N_3, or

16) F.

Preferably, R^3 is selected from: hydrogen and C_1-C_6 alkyl.

Preferably, R^4 and R^5 are hydrogen.

Preferably, R^6, R^7 and R^{7a} is selected from: hydrogen, unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

Preferably, R^{6a} is unsubstituted or substituted C_1-C_6 alkyl, unsubstituted or substituted aryl and unsubstituted or substituted cycloalkyl.

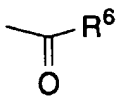
Preferably, R^9 is hydrogen or methyl. Most preferably, R^9 is hydrogen.

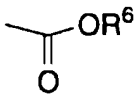
Preferably, R^{10} is selected from H, C_1-C_6 alkyl and substituted and unsubstituted benzyl.

Preferably, R^{12} is selected from: H; unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocycle,

wherein the substituted alkyl, suvbstituted aryl or substituted heterocycle is substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a) C_{1-4} alkyl,
   b) halogen,
   c) CN,
   d) perfluoro-C_{1-4} alkyl,
2) C_{3-6} cycloalkyl,
3) OR^6,
4) SR^{6a}, $S(O)R^{6a}$, or SO_2R^{6a},

5) 

6) 

7) N_3,

8) F,

9) perfluoro-C_{1-4}-alkyl, or

10) C_{1-6}-alkyl.

Preferably, A^1 and A^2 are independently selected from: a bond, -C(O)NR^{10}-, -NR^{10}C(O)-, O, -N(R^{10})-, -S(O)2N(R^{10})- and-N(R^{10})S(O)2-.

Preferably, V is selected from hydrogen, heterocycle and aryl. More preferably, V is phenyl.

Preferably, X^1 is a bond.

Preferably, X^2 is a bond, -CH_2-, -C(=O)-, -NR^6C(=O)-, -C(=O)NR^6- or -S(=O)m-.

Preferably, Y is selected from hydrogen, R^{10}O-, R^{10}C(O)NR^{10}-, (R^{10})2N-C(O)-, R^{12}C(O)-, R^{10}OC(O)-, -N(R^{10})2, and unsubstituted or substituted C_1-C_6 alkyl. More preferably, Y is R^{10}O-, R^{10}OC(O)- and unsubstituted or substituted C_1-C_6 alkyl.

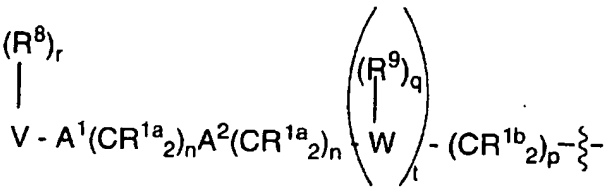
Preferably, Z is selected from unsubstituted or substituted phenyl, unsubstituted or substituted naphthyl, unsubstituted or substituted pyridyl, unsubstituted or substituted furanyl and unsubstituted or substituted thienyl. More preferably, Z is unsubstituted or substituted phenyl or unsubstituted or substituted naphthyl.

Preferably, W is selected from imidazolinyl, imidazolyl, oxazolyl, pyrazolyl, pyrrolidinyl, thiazolyl and pyridyl. More preferably, W is selected from imidazolyl and pyridyl.

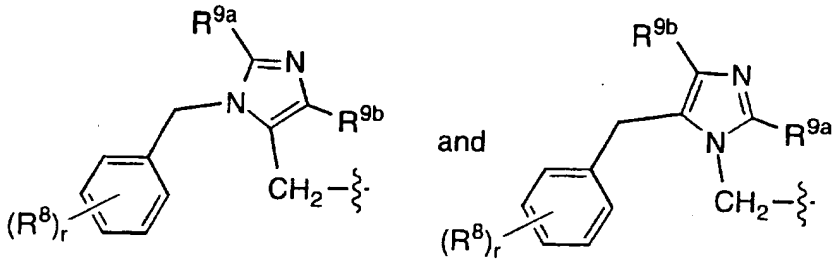
Preferably, n and r are independently 0, 1, or 2.

Preferably p is 1, 2 or 3.

Preferably s is 0.
Preferably t is 1.
Preferably, the moiety



is selected from:



It is intended that the definition of any substituent or variable (e.g., R1a, R^9, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R^{10})2 represents -NHH, -$NHCH_3$, -NHC_2H_5, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic,